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# Stereochemical studies on arylsubstituted carboxylic acids with special reference to the relationship between the optical rotatory dispersion and configuration

By Berndt Sjöberg

With 2 figures in the text

## Introduction

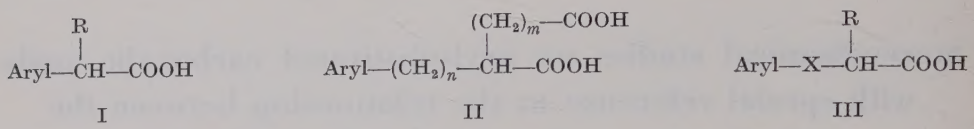
The importance of stereochemical factors in biological processes has been recognized since Pasteur [12] demonstrated in 1857 that certain moulds decompose largely the dextrorotatory component of salts of DL-tartaric acid so that the remaining levorotatory form can be isolated. The general specificity of enzymes has been widely studied, and enzyme specificity is regarded as "one of the most important biological phenomena, without which the ordered metabolism of living matter would not exist and life itself would be impossible" [13]. Enzymes are not only structurally specific; they also show steric specificity when they act upon, or form asymmetric substances. The influence of stereochemical factors upon biologically active compounds has received great attention and has been especially studied on antigen-antibody systems [14], on plant growth regulators [15, 16, 17] and on drugs [18, 19], and it can be expected that stereochemical studies will be increasingly used to help to elucidate the mechanism of drug action.

Stereochemical studies have been of great importance in the elucidation of the mechanism of several chemical reactions [20, 21, 22] and the detailed path of the reactions could be discovered only because the stereochemistry of the reactants, as well as of the products, was known.

Configurational determinations are fundamental problems in stereochemistry, and several chemical, biological and physical methods have been developed for correlation of relative configurations [23, 24]. The absolute configuration of glyceraldehyde is known from the X-ray crystallographic investigations by Bijvoet *et al.* [25], and consequently the absolute configuration will be known for any compound related to glyceraldehyde. Using chemical methods, the steric relationship between two compounds may be correlated either by reactions that do not involve the asymmetric centre or at the asymmetric centre by reactions that are known to be stereospecific. It is, however, often more convenient to use physical methods, and several correlations have been deduced from the study of optical rotations at the sodium D-line [24, 26]. It is obvious that more reliable results will be obtained if the comparisons of the molecular rotations are performed at several wavelengths, or even better, if the optical rotatory dispersion curves are compared over as wide a wavelength range

as possible. It has also been clearly demonstrated by Djerassi *et al.* [27, 28, 29] that optical rotatory dispersion studies are simple and extremely useful for stereochemical assignments of ketones and aldehydes.

A great number of optically active carboxylic acids of the following types,



I II III

where X is $CH_2$, NH, O, S or Se, have for various reasons been studied at this Institute [6–8, 16, 30, 31]. The purpose of these and previously reported investigations [1–11] has been to study carboxylic acids of types I–III, and to establish how optical rotatory dispersion curves can be used in configurational assignments of these compounds.

The stereospecificity of enzymes has been of great value in establishing the configuration of for example amino acids, hydroxy acids and sugars [32]. It has also been shown that plant growth substances of the structure III, where X is NH, O or S, usually have a stereospecific action [16, 17]. When the stereospecificity has been sufficiently demonstrated for compounds of a certain type, conclusions about the steric relationship may be drawn from a study of their biological effects [33]. Some new carboxylic acids of type I have been studied in order to see whether plant growth regulators of even this type are stereospecific in their action, so that biological tests could be more generally used in stereochemical correlations.

## Methods of preparation

In order to realize the plan outlined above, it was necessary to prepare some optically active compounds of type I and also to include arylselenoalkylcarboxylic acids in the studies of compounds of type III. Hydratropic acid (IV) has previously been investigated by several authors (for references see [6, 34]), and the optically active forms of α-(1-naphthyl)-propionic acid (V) have been prepared by Fredga [35]. α-(4-Methyl-1-naphthyl)-propionic acid (VI) and α-(2-naphthyl)-propionic acid (VII) were obtained *via* the arylcyanoacetates [1, 5] according to the general procedure for preparation of α-arylalkylcarboxylic acids by Wideqvist [36]. This method, however, gave a low yield when it was tried for α-(3-thianaphthenyl)-propionic acid (VIII). The acid was prepared instead by selective reaction of 3-thianaphthenylmagnesium bromide with pyruvic ester to yield α-hydroxy-α-(3-thianaphthenyl)-propionic acid, and the hydroxy group then reduced with stannous chloride [2]. The synthesis had to be somewhat modified for the corresponding 2-isomer. Thianaphthene is readily metalated in the 2-position, but all attempts to react 2-thianaphthenyllithium with pyruvic ester were unsuccessful. However, the lithium compound could easily be converted directly to the Grignard compound and the subsequent steps in the synthesis of α-(2-thianaphthenyl)-propionic acid (XI) were carried out in the same way for the corresponding 3-isomer [4].

Some different methods were tried and compared for the preparation of arylselenoalkylcarboxylic acids, and it was found that these compounds can be obtained in a fair yield when arylmagnesium halides are reacted with selenium and the complex then treated with alkali and a halogen acid. The diselenides formed in these reactions

can easily be reduced with sodium borohydride in benzene-alcohol solution and then converted to the desired acids in good yields without isolation of the selenols [37].

The resolution of the acids was performed by recrystallization of the alkaloid salts, and could usually be performed without difficulty after careful preliminary experiments with several bases and solvents. In the case of α-(2-thianaphthenyl)-propionic acid the levorotatory form could only be obtained in a satisfactory way from the salt with α-(2-naphthyl)-ethylamine [4]. This amine is generally very useful as a resolving base [38]. The optically active forms of α-(3-indolyl)-propionic acid (IX) has previously been prepared by Kögl and Verkaaik [39] from the quinine and cinchonine salts; with this method it was difficult to obtain the levorotatory acid, but it was found that both antipodes could be isolated in good yield using brucine and cinchonidine [3]. Cinchonidine has also been shown [40] to be the most suitable base for preparation of (−)-α-(1-methyl-3-indolyl)-propionic acid (X).

## Stereochemical correlations

Before a new method can be used for stereochemical correlations, it must, of course, have been tested on an adequate series of compounds. The same precautions must also be taken when an empirical method, which is already well established for a certain type of compounds, is to be used for new types. It is desirable to check the method on a large number of compounds in the different series, and it is imperative to know the stereochemistry of the test substances. The configurations of most of the substances of type II and III were already known from previous determinations by other investigators (for references, see [9, 10]), while the configurations of several arylakylcarboxylic acids had to be established by the author. In these determinations both chemical and physical methods have been employed.

### *Chemical methods*

Steric correlations by chemical reactions not involving the asymmetric centre was the first method used for determination of relative configurations. Freudenberg [23] employed the method extensively to establish relationships between sugars and hydroxy acids, and Levene *et al.* [41, 42, 43] to several carboxylic acids and the corresponding alcohols, halides and hydrocarbons. Introduction of tosyl esters, which can be cleaved easily to hydrocarbons with lithium aluminum hydride, in work on correlations has afforded a valuable means of relating alcohols to hydrocarbons [44] and amino acids *via* amino alcohols to amines [45]. The method is very versatile and has for example been used in a direct chemical interrelation of the configuration of terpenes and hydroxy acids [46]. It was shown already in 1940 that several sulphur compounds can be easily desulphurized with Raney nickel [47], and the method, applied to thioketals and thioacetals, has proved to be especially valuable when a keto group has to be converted to a methylene group in molecules with other vulnerable groups and it has often been used for correlations among the steroids [48]. Fredga [49] showed that optically active thiophene compounds could be desulphurized with Raney nickel to the corresponding aliphatic substances without racemization. Since the configuration of phenyl and thienyl compounds can often be related by means of the quasi-racemate method [30, 50–53], the desulphurization provides a very useful method for the correlation of aromatic and aliphatic compounds. Using

this method α-(2-thianaphthenyl)-propionic acid (XI) was converted to α-methyl-γ-phenylbutyric acid (XII), and the latter acid could be ozonized to α-methylglutaric acid (XIII) of known configuration [4].

The configurational relationship between α-(3-indolyl)-propionic acid (IX) and α-(1-methyl-3-indolyl)-propionic acid (X) could be established by direct methylation in liquid ammonia [8], using a similar procedure as employed by Fredga and Agenäs [40] for the preparation of racemic α-(1-methyl-3-indolyl)-propionic acid. It is well known that phenylacetic acid, its esters, or similar compounds are alkylated at the α-carbon by alkyl halides in the presence of alkali amides in liquid ammonia [54, 55], and that the amide effects an immediate ionization of the α-hydrogen [54]. In the case of methyl α-(3-indolyl)-propionate, the hydrogen attached to the indole nitrogen will presumably first react with the sodium amide, and racemization can be expected to be avoided if there is an excess of ester in relation to the base present. It was also shown [8], that under these conditions (+)-methyl α-(3-indolyl)-propionate could be converted to (+)-methyl α-(1-methyl-3-indolyl)-propionate without any racemization.

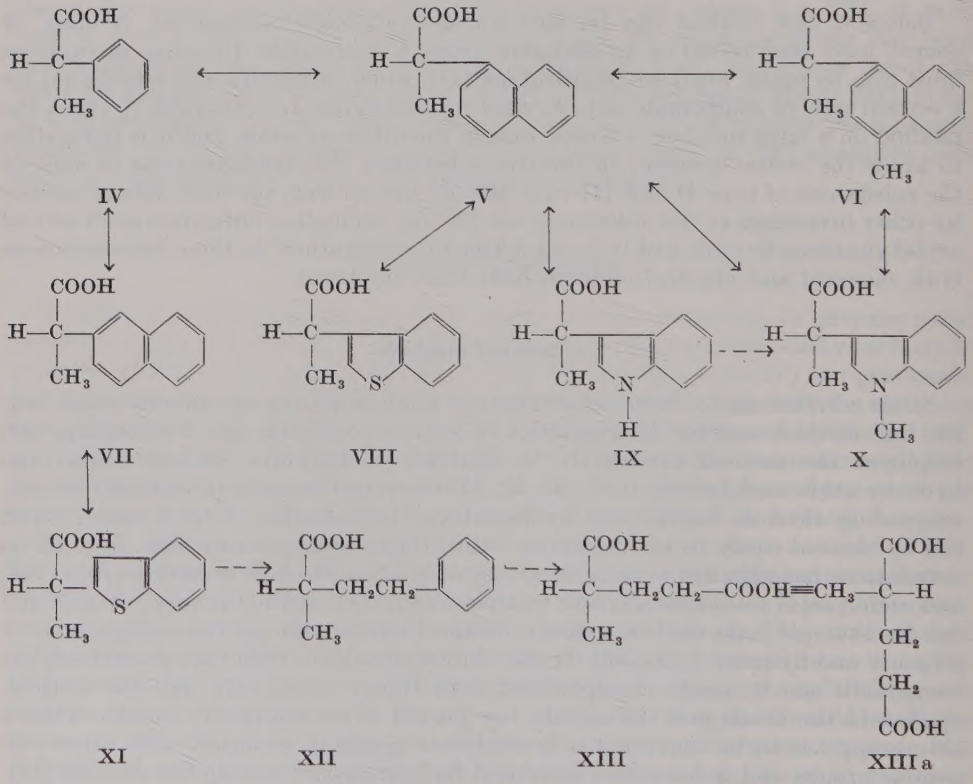



Fig. 1. Sterically related acids; all are dextrorotatory in ethanol. Solid arrows indicate relationships obtained by the quasi-racemate method, and the dotted arrows refer to chemical methods.

Displacement reactions involving the asymmetric centre have often been used in establishing the configurational relationships between optically active compounds

[20, 21]. The extensive investigations by Hughes, Ingold and collaborators [20] have shown that a bimolecular displacement reaction ($S_N2$) always involves inversion of configuration, while unimolecular substitution ($S_N1$) may involve inversion, racemization or retention. It is thus evident that displacement reactions involving the asymmetric centre cannot be definitely reliable for correlations, unless they are kinetically studied. α-Bromopropionic acid has been studied under various conditions, and it has been found that the reaction with an hydroxide ion is bimolecular and proceeds with inversion of the configuration [20]. As dextrorotatory α-phenylthiopropionic acid can be obtained from L-(−)-α-bromopropionic acid and sodium thiophenolate [56] it should have the D-configuration; further evidence for this configurational assignment has been given by the author [10].

### *Biological methods*

Biologically active substances, with the exception of some very simple ones, are structurally and usually also sterically specific in their action. These substances exert their activity as result of interaction with specific receptors, such as enzyme systems, and it is generally assumed that the first step is the formation of a complex (receptor-substrate complex) which subsequently breaks down to give free receptor and the products of the reaction. The dissociation constants of the complexes are dependent on the "closeness of fit" between the substrate and the receptor, and stereospecificity is an obvious consequence of the need for accurate spatial correspondence between the combining groups of the receptor and those of the substrate.

Investigation of enzyme specificity may give results which are difficult to interpret if the work has not been performed on pure enzymes and substrates [13], but nevertheless, enzymatic evidence has been successfully used in the determination of the configuration of amino acids, hydroxy acids and sugars [32]. When a substrate acts on a complex biological system (*in vivo* experiments) it may be difficult to judge if the observed activity is directly related to the receptor-substrate reaction at the primary active site, as the distribution as well as the adsorption of the enantiomers at complementary surfaces are stereochemically dependent [19].

The influence of stereochemical factors on plant growth substances first received attention in 1935 when Haagen-Smit and Went [57] found a difference in the activity between *cis*- and *trans*-cinnamic acid. Two years later Kögl [58] studied the effect of optical isomers and showed that the (+)-form of α-(3-indolyl)-propionic acid is about 30 times more active than the (−)-form in the *Avena curvature test*. In later experiments by Kögl and Verkaaik [39] it was found that both antipodes gave identical results in the *Avena cylinder test*, and it was suggested that the difference in activity between the enantiomers in the *curvature test* was due to differentiated transport caused by adsorption on some asymmetric compound in the coleoptile. Later investigations in this field (for a general review see references 59, 60), particularly by Fredga, Matell and Åberg [16, 17, 61] on a great number of aryloxyalkylcarboxylic acids have shown that the (+)- and the (−)-antipodes usually have significantly different activity even in those tests where transport differences do not seem to play a major role. The configurations of these aryloxyalkylcarboxylic acids were determined and it was found that the enantiomers with the greater auxin activity always have the D-configuration. Conclusions about the configuration of compounds of this series can thus be drawn from a study of the biological effects [16, 33].

A reinvestigation of the plant growth regulating effects of the optically active forms of α-(3-indolyl)-propionic acid was of considerable interest as most of the other enantiomeric plant growth regulators showed distinct differences in the activity, even in those tests where transport effects should be small. In order to see whether there is a general connection between auxin activity and steric configuration of optically active plant growth substances, and also to establish if the more active enantiomers belong to the D-series even for arylalkylcarboxylic acids, a joint work was undertaken by Professor B. Åberg (Royal Agricultural College) and the author. Substances similar in structure to α-(3-indolyl)-propionic acid were chosen so that it should be possible to establish the steric relationship between them by means of the quasi-racemate method and further connect them to the glyceraldehyde system (see Fig. 1). The chemical part of these investigations is described by the author [1–6, 8] and the plant physiological results for some of the compounds by Åberg [62, 63]. In the series of aryloxyalkycarboxylic acids, the L-forms always had anti-auxin effects or were inactive [16, 17], while in the series of arylalkylcarboxylic acids both the D- and the L-forms can have typical auxin activity. In the *Avena cylinder test* the activity is usually higher for the D-forms, but the difference can be negligible as for α-(3-indolyl)-propionic acid; in the *flax root test* the acids of L-configuration may have even higher activities than their enantiomers [6, 62, 63]. The stereospecificity of optically active plant growth substances can thus not be considered to be absolute, but must be related instead to the molecular structure as a whole [62]. Configurational assignments obviously cannot with certainty be based on plant physiological tests unless the compounds belong to series for which it has been rigorously proved that the action is stereospecific.

## *Physical methods*

### *The quasi-racemate method*

Stereochemical correlations may often be conveniently made by physical methods, as in studies of optical rotations, from X-ray or electron diffraction investigations, from different spectrometric methods or from phase properties of compounds [64]. The Fredga quasi-racemate method [65, 66] proved to be extremely useful for determination of the absolute configurations of the investigated arylalkylcarboxylic acids. The steric relationships are shown in Fig. 1, where the solid arrows indicate correlations made by the quasi-racemate method, and the dotted arrows refer to chemical methods.

The quasi-racemate method has been extensively investigated and discussed [16, 30, 65, 66], and it has been found that structural differences between the components must not be too great for the formation of the quasi-racemic compound. It is also more easy to obtain a quasi-racemate if both, or at least one, of the components have a true racemate of great stability. Attempts to relate racemate formation tendency to general properties of a substance have been made by different investigators. Landrieu [67] proposed that compounds which can form ions should tend to form true racemates. Ross and Somerville [68] assumed that the stability of the racemate was related to the degree of association; strongly associated compounds should form racemates. Notable exceptions have been found, for example by Matell [69] with β-oxy-β-phenylpivalic acid, and by Bickel and Peaslee [70] on β-benzoylhydratropic acid. In these cases the acids give conglomerates while the methyl esters give true

racemates. The stability of racemates often varies considerably even in homologous series; for example between α-xauthogen-propionic and -butyric acids [65, 66], and between alkylphenylacetamides [30]. Similarly it has been found that the racemate formation tendency for α-(1-naphthyl)-propionic and α-(3-thianaphthenyl)-propionic acids is very great, while it is rather small for the structurally similar α-(3-indolyl)-propionic acid [3, 6]. It was then assumed that hydrogen bonds, from the hydrogen bound to the hetero atom in the indol nucleus, cause, in some way, the low stability. Methylation at this position also changed the features of the melting point curve and α-(1-methyl-3-indolyl)-propionic acid was found to have a much greater racemate formation tendency than α-(3-indolyl)-propionic acid [8].

The stability of a racemate (or if it is considered as "eine singuläre Mischphase" [71]) is obviously dependent on the possibilities for favourable packing in the lattice of the D- and the L-forms in a D:L = 1:1 composition. It is difficult to view and predict in what way dipole interaction and molecular packing will be different for the antipodes and the corresponding racemate. The reason why one substance has a great racemate formation tendency and a similar one has low tendency, can probably not be fully understood until the crystal structures have been solved for the racemates as well as for the antipodes of some series of compounds. Such structure determinations have recently been carried out by Abrahamsson who studied the solid state behaviour of optically active and racemic 2-methyloctadecanoic acid [72].

Demonstration of a quasi-racemate between two structurally related compounds provides an elegant and safe proof of opposite configuration of the components, but a study of the phase behaviour can be successful for stereochemical correlations even if quasi-racemates are not formed [73, 74]. Formation of a solid solution of one isomer with only a single isomer of the other compound will indicate like configurations for the two isomers which are mutually soluble in the solid state. If the mixtures of one isomer with both isomers of the other substance show similar phase behaviour, i.e. if both mixtures form simple eutectics, compounds or solid solutions, it is not safe to draw conclusions about the steric relationship from the melting point diagrams. It has, however, often been observed that compounds of opposite configurations have eutectic diagrams with steeper branches than the corresponding compounds of the same configuration [75].

The phase properties of the two-component mixtures are usually studied in melting point diagrams, but the existence of a molecular compound can often be rapidly revealed on small samples by use of the contact method [76]. If it is difficult, for some reason, to interpret the melting point diagrams it is desirable to complement the study with X-ray powder photographs, and this has been extensively done by Pettersson [30] and Gronowitz [51, 77] in order to detect quasi-racemates. The X-ray diffraction method was of special value in determining the configuration of α-(3-indolyl)-propionic acid, as it was difficult to conclusively demonstrate the existence of a quasi-racemate between (+)-α-(3-indolyl)-propionic and (−)-α-(1-naphthyl)-propionic acids from the melting point diagrams [3]. Significant differences in the infrared spectra are often found in the solid state between the racemic form and the antipodes of a substance, and similarily between the equimolar mixtures forming a quasi-racemate and those forming an eutectic diagram or a solid solution [2, 78]. The infrared spectra are convenient to study, and they can be very useful in detecting quasi-racemates.

*Optical methods*

Stereochemical correlations from optical rotation data are simple to make, and the method can be successfully employed on various problems if it is used with care, and the compounds compared to a series which is truly analogous (for a review and references, see Klyne [26]). The use of the optical method is based on the application of a number of empirical rules, for example the *rule of optical superposition* (van't Hoff 1894; Guye and Gautier 1894) which states that the rotation of a compound with two or more asymmetric centres is the sum of independent, additive contributions from the different centres. The rule holds only qualitatively due to mutual vicinal action of the different centres. Nevertheless, as formulated by Hudson [79], it has had a great importance especially for the elucidation of stereochemical problems among the carbohydrates. The contribution to the rotation from a certain group rapidly decreases when the group is separated from the asymmetric centre by methylene groups. This fact was generalized by Tschugaeff [80] in the *distance rule* which states that the effect of a given structural change on the optical rotation is the smaller, the further the site of the change is from the asymmetric centre.

Reasonable evidence for the configuration of a compound may be obtained from a single measurement of rotation only if the compound belongs to a homologous series containing a single asymmetric centre, and where a group is varied which is not dominant for the rotation. According to Kuhn's *vicinal rule* [81], a substitution in one of the groups attached to the asymmetric centre will mainly cause a change in the anisotropy of this group while the vicinal action is less affected. This fact constitutes the basis for Freudenberg's *displacement rule* [82], in which the rotational shifts for series of derivatives are compared, and if two similarily constituted compounds with the same configuration are altered in the same way the shifts in molecular rotation will be in the same direction and usually of the same order of magnitude. This rule is more generally useful than rules based on single rotations, and it has been applied to numerous correlations of compounds even belonging to different classes, e.g. $\alpha$-amino acids with $\alpha$-hydroxy acids [26, 83] and steroids with terpenoids [26, 48].

*Solvent effects.*—Changes in external conditions, such as solvent, temperature and concentration, may influence the optical rotation considerably [84]. The effects are complex and difficult to treat quantitatively, but can easily be qualitatively understood and related to the different theories for optical rotation [85, 86]. It is evident that solvents which undergo chemical reactions with the solute will greatly influence the rotation unless the reacting group of the solute is far separated from the asymmetric centre. Dipole-dipole interaction might distort the structural framework of the asymmetric molecules, and the distortion will affect the optical rotation since this is very sensitive to the relative positions of the various groups and chromophores of the molecule. According to Beckmann and Cohen [85] the rotation, in a medium of constant refractive index, is linearly proportional to the electrostatic field on the active molecule. Dipole-dipole interaction between the solvent and the solute will cause changes in the local field, and in that way exert direct vicinal action on the chromophores of the optically active compound. It is then to be expected that solvents will effect similar compounds in an analogous way. Comparisons of the optical activities in different solvents have also been used for configurational correlations [6, 16, 30, 87]. These studies of the rotational shifts in different solvents can be considered as a special case of applying Freudenberg's displacement rule. It is difficult to predict how large, and exactly what kind of structural differences between com-

pounds to be compared can be tolerated when rotational shifts in different solvents are used for steric correlations. As the conformation is so important for the optical rotation [29, 88, 89], it seems to be inadvisable to use the solvent effects to compare compounds which will undergo conformational changes, unless it is shown, for example by spectroscopic methods, that the compounds undergo similar changes. The vicinal action of the solvent on a series of compounds ought to be similar if the optically active compounds have related polar properties and the resultant dipoles are in the same directions [85]. The great similarity in solvent effects of alkylphenylacetic acids found by Pettersson [30] could thus be expected. In the same way it is natural that these acids showed a different solvent dependence to the corresponding amides or anilides, and also that the series of amides, as well as the series of anilides each have a particular solvent sequence [30]. The solvent influence on the rotation of the α-arylpropionic acids IV–XI has been investigated by the author [6, 8], and it was found that α-(1-naphthyl)-, α-(4-methyl-1-naphthyl)-, α-(3-thianaphthenyl)-, α-(3-indolyl)- and α-(1-methyl-3-indolyl)-propionic acids have a similar solvent dependence and the largest rotations in benzene, while that of hydratropic acid, α-(2-naphthyl)- and α-(2-thianaphthenyl)-propionic acids is somewhat different, having the largest rotations in acetone. The directions of the resultant dipoles should be different in, for example, 1-naphthyl and 2-naphthyl derivatives, and this may be the reason for the different solvent effect; conformational effects due to steric interaction between the 1- and 8-substituents may also be important. The displacement rule is best used when the shifts are large, and conclusions about configurational relationships from the solvent effects should only be drawn when significant shifts are found. If the optically active compound has a polar group the largest shifts will be found between the rotations in a polar and a non-polar solvent, e.g. nitromethane or acetone and benzene. Considerable negative shifts have been observed for arylalkylcarboxylic acids [6, 8, 30] and aryloxyalkylcarboxylic acids [16, 90] of D-configuration when the rotation was measured in dilute sodium hydroxide solution compared to that in acetone or ethanol. However, the alkali solution is in these cases not just a solvent; measurements of the rotations for acids in alkali solution is more a conventional application of the displacement rule which give good evidence for the configurational relationships in a very convenient way.

The effect of temperature is easily understood, when the sensitivity of the optical rotation to molecular conformation is considered. On theoretical grounds it can be expected that an increase in temperature will cause a decrease in the optical rotation because higher temperatures will increase the freedom of rotation of the different groups [86]. The magnitude of the effect will be dependent on the structure of the optically active compound; substances having no bulky groups and already possessing freedom of rotation at room temperature will only have a small temperature dependence. Large temperature effects may naturally be found if the solute constitutes an equilibrium mixture of two or more distinct molecular species.

The specific rotation of a compound in a given solvent is not quite constant at a given wavelength and temperature as there will be some interaction between the solute molecules unless the rotations are measured in dilute solutions. The active molecules are surrounded by others of the same kind, and their interaction can be considered as a mutual solvent effect. The variations of the specific rotation with the concentration will then be dependent on the nature of both the optically active substance and the solvent. The concentration effect has been studied for hydratropic acid, and it was found to be noticeable in ethanol, but quite negligible in benzene

(Table 1). The acid will probably exist as a dimer in benzene at all the concentrations, but the fraction of dimers ought to decrease in alcohol at increased dilution due to the possibility of hydrogen bonding with the solvent.

*Table 1.* Specific rotation of (+)-hydratropic acid at different concentrations.

| Concentration g/100 ml | $[\alpha]_D^{25}$ benzene | $[\alpha]_D^{25}$ ethanol |
|---|---|---|
| 10.00 | 93.2° | 77.3° |
| 5.00 | 93.2° | 77.6° |
| 2.50 | 93.4° | 78.2° |
| 1.25 | 93.6° | 79.0° |
| 0.625 | 93.6° | 80.0° |

*Optical rotatory dispersion*

Studies of the optical rotatory dispersion, i.e. the change of optical rotation with wavelength, have been carried out by various scientists since the phenomenon was discovered in 1817 by Biot [91]. The earlier investigations (for reviews see references 84, 92) were mainly concerned with the physico-chemical aspects and theories of optical rotation and rotatory dispersion. It was early pointed out [23] that stereochemical correlations by means of the optical method are more reliable if optical rotatory dispersion data are used instead of rotations at a single wavelength, but due to the experimental difficulties the optical rotatory dispersion was investigated for only relatively few substances before 1954, and the method was rarely used by organic chemists as a tool for the solution of structural or stereochemical problems. The construction of a simple and commercially available spectropolarimeter [93, 94], which permitted the rapid measurement of the dispersion curves for a large number of compounds, accompanied by empirical correlations between the curves and certain structural features of the molecules, as in the case of ultraviolet and infrared spectroscopy, has been more important than theoretical advances in making these methods useful for the organic chemist. Extensive studies of the optical rotatory dispersion of ketones and aldehydes were started by Djerassi [95] in 1954, and ultraviolet spectropolarimetry has already found important applications in organic chemistry and biochemistry [27–29, 96].

A brief account of the physical background of optical rotatory dispersion and of the nomenclature has recently been given in a paper by the author [9], and references to more extensive surveys are also found there. The optical rotatory dispersion work performed recently by organic chemists has mainly been concerned with the anomalous dispersion curves of ketones and aldehydes, and it has clearly been shown that the sign, shape and amplitude of these curves can be correlated empirically to certain structural and steric features of the compounds [27–29]. The Drude equation has only been of small value in these studies, but is widely used in optical rotatory dispersion work on polypeptides and proteins [96]. It would be of interest to record the quantitative contributions to the rotation of different groups in optically active compounds, but determination of the rotational strengths from rotatory dispersion curves is very laborious [97]. The anisotropy of a certain transition can, however, be more readily calculated from the circular dichroism curves, but until suitable instruments

are available, it will probably be more profitable to empirically correlate the special features of the rotatory dispersion curves to the structure and stereochemistry of series of compounds.

In previous work [9, 10] the author investigated the optical rotatory dispersion curves for a great number of carboxylic acids of types I–III. The carboxyl group absorbs too far down into, and the aromatic group just on the border of the accessible wavelength region, and as a consequence it was only possible to determine the plain part of the dispersion curves. With the compounds investigated by Djerassi *et al.* [27–29] the useful information has been obtained mainly from the anomalous part of the dispersion curves. Thus, two different problems arose: (a) What information can be obtained from plain dispersion curves, and (b) how can compounds with plain curves be transformed into derivatives possessing anomalous dispersion curves. The plain curves were discussed in two papers [9, 10] and in another [11], it was shown that the acids could easily be converted into ketones possessing anomalous curves. Other groups than carboxyl groups can be converted into suitable derivatives, and it has recently been found [98] that dithiocarbalkoxy derivatives of α-hydroxy and α-amino acids have strongly rotating Cotton effect curves from which the configurations can be conveniently assigned.

The rotatory dispersion studies in the references 9–11 have given results of a certain general value for configurational determinations of compounds related to the structures I–III.[1] In the Aryl—$\underset{\displaystyle R}{\underset{|}{C}}$H—COOH series, where R is alkyl, analogous configurations will give very similar dispersion curves if the aryl group is kept constant and the alkyl group varied. If, on the other hand, the aryl group is varied, the magnitude of the rotation may change considerably but the dispersion curves will still be of the same general type and especially sign. The aryl group has a dominant influence on the rotation and very great variations in this group may be expected to reverse the sign of the dispersion curves, as has been found in one case in the series of aryloxyalkylcarboxylic acids (see below). However, it has been found [9] that the following variations in the aryl group have not resulted in any major rotatory dispersion changes: phenyl, *p*-aminophenyl, *p*-nitrophenyl, *p*-chlorophenyl, *p*-hydroxyphenyl, 1-naphthyl, 4-methyl-1-naphthyl, 2-naphthyl, 2-thianaphthenyl, 3-thianaphthenyl, 3-indolyl and 1-methyl-3-indolyl. Compounds in this series of D-configuration have plain positive dispersion curves.

The configurations of certain compounds belonging to the

$$\text{Aryl—(CH}_2)_n\text{—}\underset{\displaystyle (CH_2)_m\text{—COOH}}{\underset{|}{C}}\text{H—COOH}$$

series can also be conveniently determined from the dispersion curves [9]. Variations in the aryl group will ordinarily not change the sign of the dispersion curves, if $n$ is equal to 0 and $m$ kept constant. The aryl group can probably be varied in the same way, as for compounds belonging to type I (see above). When the aryl group is directly attached to the asymmetric centre, variations in $m$ will not usually change the sign of the dispersion curves, e.g. phenylsuccinic, α-phenylglutaric and α-phen-

[1] For details about the dispersion curves and references to the preparation and to configurational assignments of the compounds by other methods, the reader is referred to the papers 9–11.

yladipic acids of the D-configuration all have plain positive dispersion curves. It is difficult to predict what influence a similar change in $m$ will have if $n$ is equal to 1 or 2, but it can be expected that the succinic and glutaric acids will have different signs on their dispersion curves if $n$ is a larger integer; for instance, D-alkylsuccinic acids have plain positive dispersion curves while D-$\alpha$-alkylglutaric acids have plain negative curves [99]. When $m$ is equal to 1 and $n$ is varied, as with the investigated phenylsuccinic, benzylsuccinic and phenylethylsuccinic acids, the dispersion curves are of the same sign for analogous configurations and will be plain positive for the D-configuration. This will be true for any variation in $n$, because for larger values of $n$ the acids will become more similar to alkylsuccinic acids.

Several series of compounds related to the Aryl—X—CH(R)—COOH type have been studied in reference 10. The aryl group has a dominant influence on the rotation of these compounds. Thus, if the aryl group and X are kept constant and the alkyl group (R) is varied, only small changes will be found in the optical rotatory dispersion curves. When the aryl group is kept constant, and X varied (among NH, O, S or Se) the same sign of the dispersion curves will be found for analogous configurations. Simultaneous variations in the alkyl group have only a small influence on the rotation. Variations of the aryl group, when X is kept constant, may cause considerable changes in the magnitude of the rotations, but the dispersion curves will in most cases have the same sign for analogous configuration. Only one definite exception has been found. The dispersion curve of D-(−)-$\alpha$-(2.4-dinitrophenoxy)-propionic acid is plain negative, while all other investigated $\alpha$-aryloxyalkylcarboxylic acids of D-configuration have plain positive curves [10].

The formation of ring compounds from open chains will reduce the possibility of rotation about single bonds, and will also cause important conformation changes. It is thus obvious that ring formation may influence the optical rotation considerably. This has often been observed [86], and the rotational shifts between open and ring closed forms are used for stereochemical correlations in Hudson's lactone rule [100, 101]. Recently Brewster [102] proposed some empirical rules which allow prediction of the sign and magnitude of rotation for many types of compounds, and in these rules special emphasis has been put on ring structures, even those caused by hydrogen bonding. The optical rotatory dispersion curves of some open chain and corresponding ring closed compounds have been investigated by the author [9, 10], and it was found that the sign of the dispersion curves is reversed in the series of alkylphenylacetic acids when the alkyl group is ring closed to the ortho position so as to form a five or six membered ring [9]. Similar reversal of the sign of the dispersion curves for open and ring closed compounds is also found in the series of phenoxyalkylcarboxylic and phenylthioalkylcarboxylic acids [10]. When the rotatory dispersion curves were taken on the keto acids XIV and XV, obtained by ringclosure of phenylsuccinic acid [103] and $\alpha$-phenylglutaric acid [104] respectively, it was found that both curves were anomalous, and that the compounds of analogous configuration have Cotton effects of opposite sign (Fig. 2). This is contrary to the open chain aliphatic ketones, which seem to have Cotton effects of the same sign when one or two carbon atoms are interposed between the asymmetric centre and the keto group [105].

Several amides and anilides related to the acids of the structures I–III have been studied and it has been found that the amides in all cases have lower rotations than the corresponding acids. The anilides, except those of aryloxyalkylkarboxylic acids,

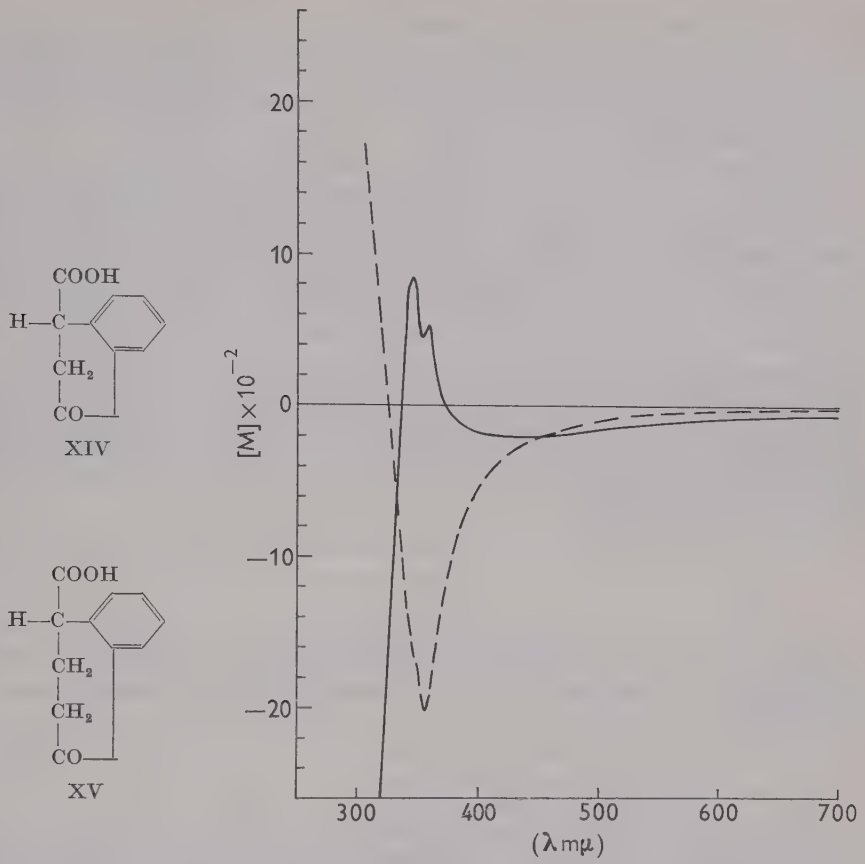



Fig. 2. Optical rotatory dispersion curves of (−)-indane-3-one-1-carboxylic acid (XIV) and (−)-1,2,3,4-tetrahydro-4-one-1-naphthoic acid (XV).

have larger rotations. In all cases the amides and anilides have the same sign on their dispersion curves as the corresponding acids, even if the sign of rotation in the visible region is often different [9, 10]. The configurational relationships between different compounds of the structures I–III can usually be obtained directly from the optical rotatory dispersion curves of the acids, but naturally the results will be even more reliable if some suitable derivatives are prepared and Freudenberg's displacement rule is applied on data obtained in the ultraviolet region or the shifts in the dispersion curves are compared [9, 10]. Anilides are then very suitable derivatives, but the simplest way is just to measure the dispersion curve of an acid in, for example, methanol and then in dilute alkali solution. Particularly large shifts in the dispersion curves between acids and their anions were found in the series of arylalkylcarboxylic acids, where measurements in alkaline solution gave dispersion curves of reversed sign compared to those of the acids measured in methanol, except for α-(1-naphthyl)-propionic and α-(4-methyl-1-naphthyl)-propionic acids [9]. The differences in rotatory behaviour, often found between 1- and 2-substituted naphthyl derivatives, is probably

due to conformational and solvent effects, and the same may also be true for the differences between benzene derivatives with free, and heavily substituted ortho positions; for example *o*-iodophenoxypropionic acid differs from the meta- and para-acids, and 2.6-dichlorophenoxypropionic acid differs somewhat from other dichlorophenoxypropionic acids [10].

It has been pointed out [10], that it is unsafe to draw conclusions about the steric relationship between compounds from the optical rotatory dispersion curves unless the measurements are extended near to the region of anisotropic absorption. Due to small rotation or high absorption of a compound it may not be feasible to carry out measurements far down in the ultraviolet region. In these cases it is desirable to prepare some derivatives which have large rotations, or even better to convert the compounds with plain curves into derivatives possessing anomalous dispersion curves in the accessible wavelength region. Some acids, both of type I and III, were converted into methyl ketones, and it was found that the compounds of D-configuration have positive Cotton effects. These ketones have very large rotations at the peak, and the configuration can conveniently be determined on only partially resolved material, or on extremely small amounts if the measurements are performed on material with high optical purity.

## Experimental

The optical rotatory dispersion curves have been obtained with a Rudolph photoelectric spectropolarimeter (the measurements were made at Wayne State University, Detroit, Michigan, U.S.A.). For details about the experimental procedure, see reference 9.

### (+)-*Indane-3-one-1-carboxylic acid (XIV)*

The acid was obtained from (−)-phenylsuccinic acid as a syrup [103], which crystallized after standing in a desiccator for several months. It was recrystallized from benzene-ligroin, m.p. 90–98°; $[\alpha]_D^{25} = +23°$, $[M]_D^{25} = +40°$ (*c* 1.00; ethanol). This product is partially racemized.

R. D. in methanol (*c* 0.105), temp. 20°: $[M]_{589} + 70°$, $[M]_{400} + 160°$, $[M]_{375} \pm 0°$, $[M]_{345} -840°$ (trough), $[M]_{310} + 4050°$. The curve in Fig. 2 refers to the enantiomer. The fine structure is typical for $\alpha,\beta$-unsaturated ketones [29], and the main Cotton effect must be related to the absorption found at 292 m$\mu$, $\varepsilon = 1130$.

### *Concentration effect on the optical rotation of hydratropic acid*

Dextrorotatory hydratropic acid (1.000 g) was diluted with the solvent (benzene and 96 % ethanol respectively) to 10.00 ml, and the optical rotation was determined in a 2 dm polarimeter tube. Dilutions were made with a 5 ml pipette, and the solvent was thermostated to 25°C at which temperature the measurements were made. The results are found in Table 1.

## SUMMARY

In this and previous papers [1–11] the preparation and resolution of a series of arylalkylcarboxylic acids have been described.

The configurational relationships have been established by means of both chemical and physical methods, and among the latter the Fredga quasi-racemate method was shown to be especially useful for these compounds.

The possibilities of using plant physiological tests in configurational assignments have been discussed, and it has been found that the method is unsafe unless the compounds belong to series for which it has been rigorously proved that the action is stereospecific.

The optical rotatory dispersion has been studied for serval acids and acid derivatives of the structures Aryl—CH(R)—COOH, Aryl—$(CH_2)_n$—CH($(CH_2)_m$—COOH)—COOH and Aryl—X—CH(R)—COOH, where X is $CH_2$, NH, O, S or Se. It has been demonstrated that the configurations usually can be obtained from the dispersion curves, and it has been discussed what variations can be made in the structure of these compounds without accompanying changes in the sign of the dispersion curves.

Some of the carboxylic acids have been converted into methyl ketones. It has been shown that the ketones of D-configuration have positive Cotton effects with very large rotations, which makes it possible to determine the configuration on material which is only partially resolved or on very small amounts of material with high optical purity.



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